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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,273	03/31/2004	Akira Ito	F-8198	7488

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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/815,273	ITO ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-6,8,9,11,12,14,19,20,23 and 33-40* is/are pending in the application.

4a) Of the above claim(s) *37 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6,8,9,12,19,20,23,33-36,39 and 40* is/are rejected.

7)☒ Claim(s) *11 and 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed April 6, 2006 in response to the Office Action of November 1, 2005, is acknowledged and has been entered. Previously pending claims 4, 5, 6, 8, 9, 11, 12, 14, 19, 20, and 23 have been amended. New claims 33-40 were added. Claims 1-3, 7, 10, 13, 15-18, 21-22, and 24-32 were canceled.

Newly submitted claims 37 and 38 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims are drawn to magnetite fine particles comprising an antibody which selectively binds to malignant tumor cells. Methods and hyperthermia agents comprising an antibody were originally part of Groups I and II of the Restriction mailed 7/27/05. Applicants confirmed election of Group III which is not drawn to magnetite fine particles comprising an antibody, in the Amendment filed April 6, 2006.

Since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 37 and 38 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 4-6, 8, 9, 11, 12, 14, 19, 20, 23, 33-36, 39, and 40 are currently being examined. It is noted Applicants stated that claims 33-41 were added (p. 11, para 1), however, there does not appear to be a new claim 41.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Objections

3. Claim 40 is objected to because of the following informalities: The claim depends on itself. Examiner believes Applicants meant to have claim 40 depend on claim 39 and will examine as such. Appropriate correction is required.

4. Claims 11 and 14 appear to be free of the art but are objected to as being dependent upon a rejected base claim, but would appear to be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

NEW REJECTION (based on new considerations)

Claim Rejections - 35 USC § 103

5. Claims 4-6, 8, 19, 20, 23, 33, 35, 39, are rejected under 35 U.S.C. 103(a) as being unpatentable over Ito et al (Cancer Gene Therapy, 2001, 8:649-654).

The claims are drawn to a method for treating a malignant tumor comprising administering cytokine to a malignant tumor and subjecting said tumor to hyperthermia (claims 19, 20), wherein hyperthermia comprises administering magnetic fine particles to said tumor and heating said magnetic fine particles (claims 4, 33), further comprising covering the magnetite with cationic liposome (claim 5, 39), wherein the cytokine is at

least one cytokine selected from the group consisting of IL-2, GMCSF, IL-4, IL-12, interferon-β, interferon-γ, and TNF-α (claims 6, 8, and 23), the method according to claim 33 wherein said magnetic fine particles comprise ferrite (claim 35).

Ito et al teach a method for treating malignant tumors by administration of magnetite cationic liposomes to the malignant tumor, administering a plasmid encoding TNF-α (a cytokine) to the tumor, and subjecting the tumor to hyperthermia (p. 650, col. 1). Ito et al teach that TNF-α was expressed as a protein (Fig. 2), confirmed by ELISA (p. 650, col. 1 to 2), and that there was a synergistic effect of TNF-α and hyperthermia combined as opposed to hyperthermia or TNF-α gene therapy alone (p. 652, col. 2; Fig 3). Ito et al teach that the magnetite is Fe_3O_4 (p. 650, col. 1). Ito et al teach that a powerful and safe treatment for tumors is possible using magnetite cationic liposomes, a plasmid encoding TNF-α, and hyperthermia (p. 653, col. 2). The reference does not specifically teach administering the TNF-α as a protein in the method of treating a malignant tumor.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat a malignant tumor by administering magnetite cationic liposomes, TNF-α, and hyperthermia to the tumor because the Ito et al specifically state that TNF-α was produced by the plasmid encoding it and contributed to the treatment of the malignant tumor in a synergistic effect. One would have a reasonable expectation of success administering TNF-α as a protein as opposed to a plasmid encoding TNF-α because the end result was the production of TNF-α protein which acted in a synergistic manner with magnetite cationic liposomes and

hyperthermia to treat malignant tumors. It was not the plasmid itself that acted in synergy. One would have been motivated to substitute TNF-α for the plasmid encoding TNF-α in the method of Ito et al because the administration of TNF-α directly would have the advantage of being administered in a form that can readily and effectively treat the tumor, as opposed to a plasmid form which requires time to translate into the effective TNF-α protein.

6. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ito et al (Cancer Gene Therapy, 2001, 8:649-654) in view of Shinkai et al I (Biotechnol Appl Biochem, 1994, 21:125-137, IDS) and Shinkai et al II (Jpn J Hyperthermic Oncol, 1994, 10:177, abstract, IDS).

The claim is drawn to a method of using cytokine and hyperthermia for treatment of a malignant tumor according to claim 33, wherein said magnetite fine particles are heated to around 43°C and maintained around 43°C.

Ito et al teach a method of using cytokine, fine magnetite particles, and hyperthermia for treatment of a malignant tumor as set forth above. Ito et al does not teach heating the magnetite particles to around 43°C and maintaining the temperature around 43°C.

Shinkai et al I teach that hyperthermia is a therapy based on the fact that the tumor cells are more sensitive to temperatures in the range of 42-45°C than normal tissue cells (abstract) and teach treating cancer by administering magnetite coated with phospholipids (magnetoliposomes) and using hyperthermia. Shinkai et al II teach

treating cancer with magnetoliposomes for hyperthermia wherein the magnetite fine particles were heated to 42-45°C (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to heat the magnetic fine particles to around 43°C and maintain at around 43°C in the method taught by Ito et al because Shinkai et al I and II both teach heating the magnetite fine particles to around 43°C for hyperthermia to treat cancer. One would have been motivated to heat the magnetite fine particles to around 43°C and maintain the temperature at around 43°C because Shinkai et al I teach that tumor cells are more sensitive to temperatures in the range of 42-45°C than normal tissue cells, hence making the tumor cells more susceptible to treatment.

NEW GROUNDS for REJECTION (necessitated by amendment)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 34 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation wherein "**maintained around 43°C**" has no clear support in the specification and the claims as originally filed. THIS IS A NEW MATTER REJECTION.

Applicants do not point out support for the amended claim. A review of the specification reveals support for heating magnetic fine particles "to around 43°C, which is generally considered to be effective in the hyperthermia within a few minutes, and **maintained at 43°C constantly** by controlling an output, whereby heating could be carried out for 30 min" (p. 12, lines 3-5). There is no clear support in the specification and the claims for maintaining the temperature **around 43°C.** The subject matter claimed in claim 34 broadens the scope of the invention as originally disclosed in the specification.

8. Claims 4-6, 8, 9, 12, 19, 20, 23, 33, 34, 35, 36, 39, and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a malignant tumor comprising: administering (a) either interleukin-2 (IL-2), granulocyte colony stimulating factor (GMCSF), or tumor necrosis factor-α (TNF-α) to a malignant tumor, (b) administering magnetic fine particles to said tumor and (c) heating said magnetic fine particles, does not reasonably provide enablement for a method for treating a malignant tumor comprising administering cytokine to a malignant tumor and subjecting said tumor to hyperthermia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some

experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for treating a malignant tumor comprising administering cytokine to a malignant tumor and subjecting said tumor to hyperthermia (claims 19, 20), wherein hyperthermia comprises administering magnetic fine particles to said tumor and heating said magnetic fine particles (claims 4, 33-36), further comprising covering the magnetite with cationic liposome (claim 5, 39, and 40), wherein the cytokine is at least one cytokine selected from the group consisting of IL-2, GMCSF, IL-4, IL-12, interferon-β, interferon-γ, and TNF-α (claims 6, 8, and 23), and the method according to claim 6 wherein the cytokine is IL-2 or GMCSF (claims 9 and 12 , respectively). Claims 4-6, 8, 19, 20, 23, 33, 34, 35, 36, 39, and 40 are broadly drawn to a method for treating a malignant tumor comprising administering **ANY** cytokine or

cytokines other than IL-2, GMCSF, and TNF-α to a malignant tumor. Claims 19, 20, 6, 9, and 12 are broadly drawn to subjecting said tumor to hyperthermia regardless of administering magnetic fine particles to said tumor.

Applicants provided an affidavit from Takeshi Kobayashi, mailed 4/6/2006, stating that the administration of magnetite fine particles and hyperthermia to a malignant tumor in addition to administration of IL-2 or GMCSF provided a synergistic effect in treating a tumor as opposed to treatment with either agent alone. Applicants state that the administration of magnetite fine particles and hyperthermia to a malignant tumor in addition to administration of IL-2 or GMCSF demonstrated a synergistic and unexpectedly improved result (p. 13, para 2 and 3; p. 14, para 2). The affidavit from Takeshi Kobayashi teaches that the tumor treatment with magnetite fine particles and hyperthermia and the addition of either IL-2 or GMCSF had an unexpectedly high anti-tumor effect (p. 6, para 3), more than the additive effects of the treatments using a single agent. Kobayashi points to Examples 1 and 2 of the specification to support the affidavit. The specification discloses that the claimed method for treating a malignant tumor is a novel therapeutic method.

The art teaches a novel method of treating a malignant tumor with magnetite fine particles, hyperthermia and TNF-α. Ito et al (Cancer Gene Therapy, 2001, 8:649-654) teach the novel method for treating malignant tumors by administration of magnetite cationic liposomes to the malignant tumor, administering a plasmid encoding TNF-α to the tumor, and subjecting the tumor to hyperthermia (p. 650, col. 1). Ito et al teach that TNF-α was expressed as a protein (Fig. 2) and that there was a synergistic effect of

TNF-α and hyperthermia combined as opposed to hyperthermia or TNF-α gene therapy alone (p. 652, col. 2; Fig 3).

One cannot extrapolate the disclosure of the specification and teachings of the Kobayashi affidavit to the scope of the claims because the specification and affidavit do not provide examples or guidance for treating malignant tumors comprising administering **any cytokine** other than IL-2, GMCSF, or TNF-α with **any form of hyperthermia** other than administering fine magnetite particles to the malignant tumor and heating said particles. Given that the results of treating a malignant tumor with fine magnetite particles, hyperthermia, and either IL-2 or GMCSF gave unexpected results in synergistic treatment of the tumor, one of skill in the art could not predictably treat a malignant tumor comprising administering any cytokine with any form of hyperthermia. Further, because the art teaches the novel and successful method of treating a malignant tumor with magnetite fine particles, hyperthermia and TNF-α, one of skill in the art could predictably treat a malignant tumor using TNF-α, as such, the art enables this specific method of treating which has synergistic results.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be reasonably predicted that a method for treating a malignant tumor comprising administering any cytokine to a malignant tumor and subjecting said tumor to any form of hyperthermia, will predictably function as claimed. Therefore, in view of the novel nature of the invention, the state of the art, the breadth of the claims, lack of guidance in the specification, and the absence of working examples,

it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

9. All other rejections and objections recited in the Office Action mailed November 1, 2005, are hereby withdrawn.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER